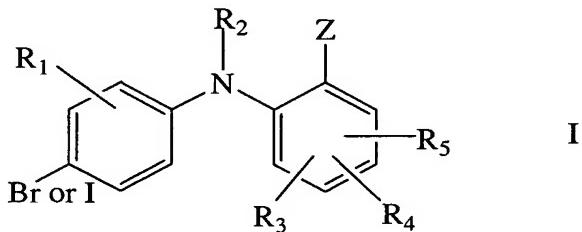


CLAIMS

What is claimed is:

1. An anticancer combination which comprises a mitotic inhibitor and a MEK inhibitor.
- 5
2. The combination according to Claim 1 wherein the MEK inhibitor is 2-(2-amino-3-methoxyphenyl)-4-oxo-4H-[1]benzopyran.
- 10
3. The combination according to Claim 1 wherein the mitotic inhibitor is selected from paclitaxel, docetaxel, vincristine, vinblastine, vinorelbine, and vinflunine.
4. The combination according to Claim 1 wherein the MEK inhibitor is a phenyl amine compound of Formula I:



15

wherein:

R₁ is hydrogen, hydroxy, C₁-C₈ alkyl, C₁-C₈ alkoxy, halo, trifluoromethyl, or CN;

R₂ is hydrogen;

20

R₃, R₄, and R₅ independently are hydrogen, hydroxy, halo, trifluoromethyl, C₁-C₈ alkyl, C₁-C₈ alkoxy, nitro, CN, or -(O or NH)_m-(CH₂)_n-R₉, where R₉ is hydrogen, hydroxy, COOH, or NR₁₀R₁₁;

n is 0-4;

m is 0 or 1;

R₁₀ and R₁₁ independently are hydrogen or C₁-C₈ alkyl, or taken together with the nitrogen to which they are attached can complete a 3-10 member cyclic ring optionally containing 1, 2, or 3 additional heteroatoms selected from O, S, NH, or N-C₁-C₈ alkyl;

Z is COOR₇, tetrazolyl, CONR₆R₇, CONHNR₁₀R₁₁, or CH₂OR₇;

R₆ and R₇ independently are hydrogen, C₁-C₈ alkyl, C₂-C₈ alkenyl, C₂-C₈ alkynyl, (CO)-C₁-C₈ alkyl, aryl, heteroaryl, C₃-C₁₀ cycloalkyl, or C₃-C₁₀ (cycloalkyl optionally containing 1, 2, or 3 heteroatoms selected from O, S, NH, or N alkyl); or R₆ and R₇ together with the nitrogen to which they are attached complete a 3-10 member cyclic ring optionally containing 1, 2, or 3 additional heteroatoms selected from O, S, NH, or N alkyl;

and wherein any of the foregoing alkyl, alkenyl, aryl, heteroaryl, heterocyclic, and alkynyl groups can be unsubstituted or substituted by halo, hydroxy, C₁-C₆ alkoxy, amino, nitro, C₁-C₄ alkylamino, di(C₁-C₄)alkylamino, C₃-C₆ cycloalkyl, phenyl, phenoxy, C₃-C₅ heteroaryl or heterocyclic radical, or C₃-C₅ heteroaryloxy or heterocyclic radical-oxy;

or a pharmaceutically acceptable salt, ester, amide, or prodrug thereof.

5. The combination according to Claim 4 wherein the MEK inhibitor is a phenyl amine selected from:
- [4-Chloro-2-(1H-tetrazol-5-yl)-phenyl(4-iodo-2-methyl-phenyl)-amine; (4-Iodo-2-methyl-phenyl)-[2-(1H-tetrazol-5-yl)-phenyl]amine; [4-Nitro-2-(1H-tetrazol-5-yl)-phenyl-(4-iodo-2-methyl-phenyl)-amine; 4-Fluoro-2-(4-iodo-2-methylphenylamino)benzoic acid; 3,4,5-Trifluoro-2-(4-iodo-2-methyl-phenylamino)-benzoic acid; 3,4-Difluoro-2-(4-iodo-2-methyl-phenylamino)-benzoic acid; 5-Bromo-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-benzoic acid; 30 5-Chloro-2-(4-iodo-2-methyl-phenylamino)-benzoic acid;

Sodium 5-Chloro-2-(4-iodo-2-methyl-phenylamino)-benzoate;
5-Bromo-2-(4-iodo-2-methyl-phenylamino)-benzoic acid;
2-(4-Iodo-2-methyl-phenylamino)-5-nitro-benzoic acid;
4-Chloro-2-(4-iodo-2-methyl-phenylamino)-benzoic acid;
5
2-(4-Iodo-2-methyl-phenylamino)-benzoic acid;
5-Fluoro-2-(4-iodo-2-methyl-phenylamino)-benzoic acid;
5-Iodo-2-(4-iodo-2-methyl-phenylamino)-benzoic acid;
2,3,5-Trifluoro-4-(4-iodo-2-methyl-phenylamino)-benzoic acid;
2-(4-Iodo-phenylamino)-5-methoxy-benzoic acid;
10
5-Methyl-2-(4-iodo-2-methyl-phenylamino)-benzoic acid;
2-(4-Iodo-2-methyl-phenylamino)-4-nitro-benzoic acid;
2-(4-Bromo-2-methyl-phenylamino)-4-fluoro-benzoic acid;
2-(2-Bromo-4-iodo-phenylamino)-5-nitro-benzoic acid;
2-(4-Bromo-2-methyl-phenylamino)-3,4-difluoro-benzoic acid;
15
5-Chloro-N-(2-hydroxyethyl)-2-(4-ido-2-methyl-phenylamino)-
benzamide;
4-Fluoro-2-(4-ido-2-methyl-phenylamino)-benzamide;
4-Fluoro-2-(4-ido-2-methyl-phenylamino)-N-methyl-benzamide;
N-Ethyl-4-fluoro-2-(4-ido-2-methyl-phenylamino)-benzamide;
20
4-Fluoro-2-(4-ido-2-methyl-phenylamino)-N,N-dimethyl-benzamide;
4-Fluoro-2-(4-ido-2-methyl-phenylamino)-N-(1H-tetrazol-5-yl)-
benzamide;
5-Bromo-2-(4-ido-2-methyl-phenylamino)-benzamide;
5-Chloro-2-(4-ido-2-methyl-phenylamino)-N,N-dimethyl-benzamide;
25
[5-Chloro-2-(4-ido-2-methyl-phenylamino)-benzoylamino]-acetic acid;
4-Fluoro-2-(4-ido-2-methyl-phenylamino)-N-propyl-benzamide;
5-Bromo-N-(2-hydroxy-ethyl)-2-(4-ido-2-methyl-phenylamino)-
benzamide;
N,N-Diethyl-4-fluoro-2-(4-ido-2-methyl-phenylamino)-benzamide;
30
4-Fluoro-N-{3-[4-(2-hydroxy-ethyl)-piperazin-1-yl]-propyl}-2-(4-ido-
2-methyl-phenylamino)-benzamide;
N,N-Diethyl-2-(4-ido-2-methyl-phenylamino)-5-nitro-benzamide;

- N-Butyl-4-fluoro-2-(4-iodo-2-methyl-phenylamino)-benzamide;
5-Chloro-N,N-diethyl-2-(4-iodo-2-methyl-phenylamino)-benzamide;
5-Bromo-2-(4-iodo-2-methyl-phenylamino)-N,N-dimethyl-benzamide;
5-Bromo-3,4-difluoro-N-(2-hydroxy-ethyl)-2-(4-iodo-2-methyl-
phenylamino)-benzamide;
- 5
N-(2,3-Dihydroxy-propyl)-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-
benzamide;
5-Bromo-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-N-(2-piperidin-1-
yl-ethyl)-benzamide;
- 10 3,4-Difluoro-N-(2-hydroxy-ethyl)-2-(4-iodo-2-methyl-phenylamino)-
benzamide;
N-(2,3-Dihydroxy-propyl)-4-fluoro-2-(4-iodo-2-methyl-phenylamino)-
benzamide;
- 15 3,4-Difluoro-N-(3-hydroxy-propyl)-2-(4-iodo-2-methyl-phenylamino)-
benzamide;
5-Bromo-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-N-(2-pyrrolidin-
1-yl-ethyl)-benzamide;
- 20 5-Bromo-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-N-(2-pyridin-4-
yl-ethyl)-benzamide;
4-Fluoro-N-(2-hydroxy-ethyl)-2-(4-iodo-2-methyl-phenylamino)-
benzamide;
- 25 5-Bromo-N-(3-dimethylamino-propyl)-3,4-difluoro-2-(4-iodo-2-methyl-
phenylamino)-benzamide;
5-Bromo-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-N-(2-morpholin-
4-yl-ethyl)-benzamide;
- 30 3,4-Difluoro-2-(4-iodo-2-methyl-phenylamino)-N-(2-morpholin-4-yl-
ethyl)-benzamide;
3,4-Difluoro-2-(4-iodo-2-methyl-phenylamino)-N-(2-pyrrolidin-1-yl-
ethyl)-benzamide;
3,4-Difluoro-2-(4-iodo-2-methyl-phenylamino)-N-(2-pyridin-4-yl-ethyl)-
benzamide;

- N-(3-Dimethylamino-propyl)-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-benzamide;
- N-Benzyl-4-fluoro-2-(4-iodo-2-methyl-phenylamino)-benzamide;
- 2-(4-Bromo-2-methyl-phenylamino)-3,4-difluoro-N-(2-hydroxy-ethyl)-
5 benzamide;
- 4-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N-(2-morpholin-4-yl-ethyl)-
benzamide;
- 4-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N-(3-piperidin-1-yl-propyl)-
benzamide;
- 10 3,4-Difluoro-2-(4-iodo-2-methyl-phenylamino)-N-(3-piperidin-1-yl-
propyl)-benzamide;
- 4-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N-(2-thiophen-2-yl-ethyl)-
benzamide;
- 4-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N-(2-pyrrolidin-1-yl-ethyl)-
benzamide;
- 15 2-(4-Bromo-2-methyl-phenylamino)-3,4-difluoro-N-(2-morpholin-4-yl-
ethyl)-benzamide;
- 5-Bromo-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-N-pyridin-4-
ylmethyl-benzamide;
- 20 3,4-Difluoro-2-(4-iodo-2-methyl-phenylamino)-N-pyridin-4-ylmethyl-
benzamide;
- 2-(4-Bromo-2-methyl-phenylamino)-N-(3-dimethylamino-
propyl)-3,4-difluoro-benzamide;
- 4-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N-pyridin-4-ylmethyl-
benzamide;
- 25 4-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N-(2-pyridin-4-yl-ethyl)-
benzamide;
- 2-(4-Bromo-2-methyl-phenylamino)-3,4-difluoro-N-(2-pyridin-4-yl-ethyl)-
benzamide;
- 30 2-(4-Bromo-2-methyl-phenylamino)-3,4-difluoro-N-(3-hydroxy-propyl)-
benzamide;

- 2-(4-Bromo-2-methyl-phenylamino)-3,4-difluoro-N-(2-pyrrolidin-1-yl-
ethyl)-benzamide;
- 4-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N-phenethyl-benzamide;
- 2-(4-Bromo-2-methyl-phenylamino)-3,4-difluoro-N-(2-thiophen-2-yl-
ethyl)-benzamide;
- 5
2-(4-Bromo-2-methyl-phenylamino)-3,4-difluoro-N-pyridin-4-ylmethyl-
benzamide;
- 2-(4-Bromo-2-methyl-phenylamino)-3,4-difluoro-N-phenethyl-benzamide;
- 2-(4-Bromo-2-methyl-phenylamino)-3,4-difluoro-N-(2-piperidin-1-yl-
ethyl)-benzamide;
- 10
5-Chloro-N-{3-[4-(2-hydroxy-ethyl)-piperazin-1-yl]-propyl}-2-(4-ido-2-
methyl-phenylamino)-benzamide;
- 5-Fluoro-N-{3-[4-(2-hydroxy-ethyl)-piperazin-1-yl]-propyl}-2-(4-ido-2-
methyl-phenylamino)-benzamide;
- 15
2-(4-Iodo-2-methyl-phenylamino)-5-nitro-N-pyridin-4-yl methyl-
benzamide;
- 5-Bromo-N-{3-[4-(2-hydroxy-ethyl)-piperazin-1-yl]-propyl}-2-(4-ido-2-
methyl-phenylamino)-benzamide;
- 5-Chloro-N-(2-diethylamino-ethyl)-2-(4-ido-2-methyl-phenylamino)-
20
benzamide;
- 5-Chloro-2-(4-ido-2-methyl-phenylamino)-N-(2-piperidin-1-yl-ethyl)-
benzamide;
- (3-Hydroxy-pyrrolidin-1-yl)-[2-(4-ido-2-methyl-phenylamino)-5-nitro-
phenyl];
- 25
5-Chloro-2-(4-ido-2-methyl-phenylamino)-N-(2-pyrrolidin-1-yl-ethyl)-
benzamide;
- 5-Bromo-N-(2-diethylamino-ethyl)-2-(4-ido-2-methyl-phenylamino)-
benzamide;
- N-{2-[Bis-(2-hydroxy-ethyl)-amino]-ethyl}-5-chloro-2-(4-ido-2-methyl-
30
phenylamino)-benzamide;
- N-{2-[Bis-(2-hydroxy-ethyl)-amino]-ethyl}-5-bromo-2-(4-ido-2-methyl-
phenylamino)-benzamide;

- N-{3-[4-(2-Hydroxy-ethyl)-piperazin-1-yl]-propyl}-2-(4-iodo-2-methyl-phenylamino)-benzamide;
- 5-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N-pyridin-4-ylmethyl-benzamide;
- 5-Bromo-2-(4-iodo-2-ethyl-phenylamino)-N-(2-pyrrolidin-1-yl-ethyl)-benzamide;
- 5-Bromo-2-(4-iodo-2-methyl-phenylamino)-N-(2-piperidin-1-yl-ethyl)-benzamide;
- 5-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N-(2-pyrrolidin-1-yl-ethyl)-benzamide;
- 5-Chloro-N-(3-dimethylamino-propyl)-2-(4-iodo-2-methyl-phenylamino)-benzamide;
- N-{2-[Bis-(2-hydroxy-ethyl)-amino]-ethyl}-5-fluoro-2-(4-iodo-2-methyl-phenylamino)-benzamide;
- 5-Chloro-N-(3-hydroxy-propyl)-2-(4-iodo-2-methyl-phenylamino)-benzamide;
- 5-Chloro-N-(3-diethylamino-2-hydroxy-propyl)-2-(4-iodo-2-methyl-phenylamino)-benzamide;
- 5-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N-(2-piperidin-1-yl-ethyl)-benzamide;
- 5-Bromo-N-(3-hydroxy-propyl)-2-(4-iodo-2-methyl-phenylamino)-benzamide;
- 5-Bromo-2-(4-iodo-2-methyl-phenylamino)-N-(3-piperidin-1-yl-propyl)-benzamide;
- N-{2-[Bis-(2-hydroxy-ethyl)-amino]-ethyl}-2-(4-iodo-2-methyl-phenylamino)-5-nitro-benzamide;
- 5-Chloro-2-(4-iodo-2-methyl-phenylamino)-N-(2-morpholin-4-yl-ethyl)-benzamide;
- 5-Chloro-N-(3-diethylamino-propyl)-2-(4-iodo-2-methyl-phenylamino)-benzamide;
- 5-Chloro-N-(2-diisopropylamino-ethyl)-2-(4-iodo-2-methyl-phenylamino)-benzamide;

- 5-Chloro-2-(4-iodo-2-methyl-phenylamino)-N-(3-piperidin-1-yl-propyl)-benzamide;
- 2-(4-Iodo-2-methyl-phenylamino)-5-nitro-N-(2-piperidin-1-yl-ethyl)-benzamide;
- 5-Bromo-2-(4-iodo-2-methyl-phenylamino)-N-(2-piperazin-1-yl-ethyl)-benzamide;
- N-(2-Diethylamino-ethyl)-5-fluoro-2-(4-iodo-2-methyl-phenylamino)-benzamide;
- 5-Bromo-N-(3-dimethylamino-propyl)-2-(4-iodo-2-methyl-phenylamino)-benzamide;
- N-(3-Hydroxy-propyl)-2-(4-iodo-2-methyl-phenylamino)-5-nitro-benzamide;
- 5-Fluoro-N-(3-hydroxy-propyl)-2-(4-iodo-2-methyl-phenylamino)-benzamide;
- N-(3-Diethylamino-propyl)-5-fluoro-2-(4-iodo-2-methyl-phenylamino)-benzamide;
- N-(3-Diethylamino-propyl)-2-(4-iodo-2-methyl-phenylamino)-5-nitro-benzamide;
- 5-Bromo-2-(4-iodo-2-methyl-phenylamino)-N-(2-morpholin-4-yl-ethyl)-benzamide;
- 2-(4-Iodo-2-methyl-phenylamino)-5-nitro-N-(3-piperidin-1-yl-propyl)-benzamide;
- [5-Fluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-[3-hydroxy-pyrrolidin-1-yl]-methanone
- 5-Bromo-N-(2-diisopropylamino-ethyl)-2-(4-iodo-2-methyl-phenylamino)-benzamide;
- 5-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N-(2-morpholin-4-yl-ethyl)-benzamide;
- 5-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N-(3-piperidin-1-yl-propyl)-benzamide;
- [5-Fluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-[4-(2-hydroxy-ethyl)-piperazin-1-yl]-methanone;

N-(3-Diethylamino-2-hydroxy-propyl)-5-fluoro-2-(4-ido-2-methyl-phenylamino)-benzamide;

N-Cyclopropyl-5-fluoro-2-(4-ido-2-methyl-phenylamino)-benzamide;

5-Chloro-N-(2-hydroxy-ethyl)-2-(4-ido-2-methyl-phenylamino)-

5 benzamide;

5-Fluoro-N-(2-hydroxy-ethyl)-2-(4-ido-2-methyl-phenylamino)-

benzamide;

N-Benzyl-5-fluoro-2-(4-ido-2-methyl-phenylamino)-benzamide;

N-Benzyl-5-bromo-2-(4-ido-2-methyl-phenylamino)-benzamide;

10 . 2-(4-Iodo-2-methyl-phenylamino)-5-nitro-N-(4-sulfamoyl-benzyl)-

benzamide;

5-Bromo-N-(2-hydroxy-ethyl)-2-(4-ido-2-methyl-phenylamino)-

benzamide;

N-(2-Hydroxy-ethyl)-5-iodo-2-(4-ido-2-methyl-phenylamino)-benzamide;

15 N-(2-Hydroxy-ethyl)-2-(4-ido-2-ethyl-phenylamino)-5-nitro-benzamide;

2-(4-Iodo-2-methyl-phenylamino)-N-methyl-5-nitro-N-phenyl-benzamide;

5-Chloro-N-cyclopropyl-2-(4-ido-2-methyl-phenylamino)-benzamide;

5-Fluoro-2-(4-ido-2-methyl-phenylamino)-N-methyl-N-phenyl-

benzamide;

20 N-Allyl-5-fluoro-2-(4-ido-2-methyl-phenylamino)-benzamide;

N-Benzyl-5-iodo-2-(4-ido-2-methyl-phenylamino)-benzamide;

5-Fluoro-2-(4-ido-2-methyl-phenylamino)-N-(4-sulfamoyl-benzyl)-

benzamide;

N-Allyl-5-chloro-2-(4-ido-2-methyl-phenylamino)-benzamide;

25 N-Cyclopropyl-2-(4-ido-2-methyl-phenylamino)-5-nitro-benzamide;

5-Bromo-N-cyclopropyl-2-(4-ido-2-methyl-phenylamino)-benzamide;

5-Chloro-2-(4-ido-2-methyl-phenylamino)-N-methyl-N-phenyl-

benzamide;

5-Iodo-2-(4-ido-2-methyl-phenylamino)-N-(4-sulfamoyl-benzyl)-

30 benzamide;

5-Bromo-2-(4-ido-2-methyl-phenylamino)-N-(4-sulfamoyl-benzyl)-

benzamide;

N-Allyl-2-(4-iodo-2-methyl-phenylamino)-5-nitro-benzamide;
2-(4-Iodo-2-methyl-phenylamino)-5-nitro-N-(4-sulfamoyl-benzyl)-
benzamide;

5

N-Allyl-5-bromo-2-(4-iodo-2-methyl-phenylamino)-benzamide;
5-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N-(3-methyl-benzyl)-
benzamide;

N-Cyclopropyl-5-iodo-2-(4-iodo-2-methyl-phenylamino)-benzamide;
5-Bromo-2-(4-iodo-2-methyl-phenylamino)-N-methyl-N-phenyl-
benzamide;

10

N-Benzyl-2-(4-iodo-2-methyl-phenylamino)-5-nitro-benzamide;
N-Cyclohexyl-5-iodo-2-(4-iodo-2-methyl-phenylamino)-benzamide;
N-Allyl-5-iodo-2-(4-iodo-2-methyl-phenylamino)-benzamide;
5-Iodo-2-(4-iodo-2-methyl-phenylamino)-N-(3-methyl-benzyl)-benzamide;
2-(4-Iodo-2-methyl-phenylamino)-N-(3-methyl-benzyl)-5-nitro-
benzamide;

15

5-Iodo-2-(4-iodo-2-methyl-phenylamino)-N-methyl-N-phenyl-benzamide;
N-Cyclohexyl-5-fluoro-2-(4-iodo-2-methyl-phenylamino)-benzamide;
5-Chloro-N-cyclohexyl-2-(4-iodo-2-methyl-phenylamino)-benzamide;
5-Bromo-2-(4-iodo-2-methyl-phenylamino)-N-(3-methyl-benzyl)-
benzamide;

20

5-Bromo-N-cyclohexyl-2-(4-iodo-2-methyl-phenylamino)-benzamide;
5-Chloro-2-(4-iodo-2-methyl-phenylamino)-N-(3-methyl-benzyl)-
benzamide;

N-Cyclohexyl-2-(4-iodo-2-methyl-phenylamino)-5-nitro-benzamide;

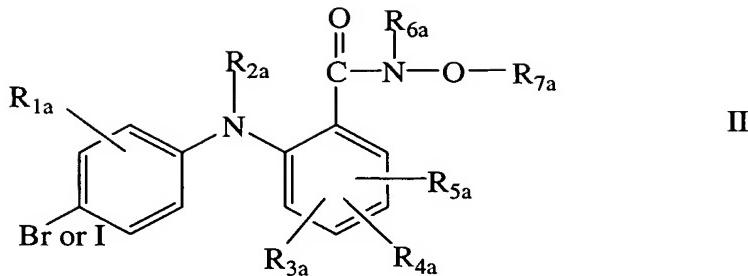
25

N-Benzyl-5-bromo-2-(4-iodo-2-methyl-phenylamino)-benzamide;
N-Benzyl-5-fluoro-2-(4-iodo-2-methyl-phenylamino)-benzamide;
5-Chloro-N-(2-hydroxy-ethyl)-2-(4-iodo-2-methyl-phenylamino)-
benzamide;

30

5-Bromo-N-(2-hydroxy-ethyl)-2-(4-iodo-2-methyl-phenylamino)-
benzamide;
2-(4-Iodo-2-methyl-phenylamino)-N-methyl-5-nitro-N-phenyl-benzamide;

- 5-Chloro-2-(4-iodo-2-methyl-phenylamino)-N-methyl-N-phenylbenzamide;
- N-(2-Hydroxy-ethyl)-5-iodo-2-(4-iodo-2-methyl-phenylamino)-benzamide;
- 5-Chloro-N-cyclopropyl-2-(4-iodo-2-methyl-phenylamino)-benzamide;
- 5
- N-Allyl-5-chloro-2-(4-iodo-2-methyl-phenylamino)-benzamide;
- 5-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N-methyl-N-phenylbenzamide;
- N-(2-Hydroxy-ethyl)-2-(4-iodo-2-methyl-phenylamino)-5-nitrobenzamide;
- 10
- 5-Fluoro-N-(2-hydroxy-ethyl)-2-(4-iodo-2-methyl-phenylamino)-benzamide;
- 5-Bromo-N-cyclopropyl-2-(4-iodo-2-methyl-phenylamino)-benzamide;
- N-Cyclopropyl-5-fluoro-2-(4-iodo-2-methyl-phenylamino)-benzamide;
- 5-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N-(4-sulfamoyl-benzyl)-
- 15
- benzamide;
- N-Cyclopropyl-2-(4-iodo-2-methyl-phenylamino)-5-nitro-benzamide;
- N-Allyl-5-fluoro-2-(4-iodo-2-methyl-phenylamino)-benzamide;
- N-Benzyl-5-iodo-2-(4-iodo-2-methyl-phenylamino)-benzamide;
- N-Allyl-5-bromo-2-(4-iodo-2-methyl-phenylamino)-benzamide;
- 20
- 5-Bromo-2-(4-iodo-2-methyl-phenylamino)-N-(4-sulfamoyl-benzyl)-benzamide;
- 5-Bromo-2-(4-iodo-2-methyl-phenylamino)-N-methyl-N-phenylbenzamide;
- N-Allyl-2-(4-iodo-2-methyl-phenylamino)-5-nitro-benzamide;
- 25
- 4-Fluoro-2-(4-iodo-2-methyl-phenylamino)-benzyl alcohol;
- [5-Chloro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-methanol;
- [2-(4-Iodo-2-methyl-phenylamino)-5-nitro-phenyl]-methanol;
- [5-Bromo-2-(4-iodo-2-methyl-phenylamino)-phenyl]-methanol; and
- N-Allyl-2-(4-iodo-2-methyl-phenylamino)-5-nitro-benzamide.
- 30
6. The combination according to Claim 1 wherein the selective MEK inhibitor is a phenyl amine of Formula II:



wherein:

R_{1a} is hydrogen, hydroxy, C₁-C₈ alkyl, C₁-C₈ alkoxy, halo, trifluoromethyl, or CN;

5 R_{2a} is hydrogen;

R_{3a}, R_{4a}, and R_{5a} independently are hydrogen, hydroxy, halo, trifluoromethyl, C₁-C₈ alkyl, C₁-C₈ alkoxy, nitro, CN, or (O or NH)_m-(CH₂)_n-R_{9a}, where R_{9a} is hydrogen, hydroxy, CO₂H or NR_{10a}R_{11a}.

n is 0-4;

10 m is 0 or 1;

R_{10a} and R_{11a} independently are hydrogen or C₁-C₈ alkyl, or taken together with the nitrogen to which they are attached can complete a 3- to 10-member cyclic ring optionally containing one, two, or three additional heteroatoms selected from O, S, NH, or N-C₁-C₈ alkyl;

15 R_{6a} is hydrogen, C₁-C₈ alkyl, (CO)-C₁-C₈ alkyl, aryl, aralkyl, or C₃-C₁₀ cycloalkyl;

R_{7a} is hydrogen, C₁-C₈ alkyl, C₂-C₈ alkenyl, C₂-C₈ alkynyl, C₃-C₁₀ (cycloalkyl or cycloalkyl optionally containing a heteroatom selected from O, S, or NR_{9a});

20 and wherein any of the foregoing alkyl, alkenyl, aryl, heteroaryl, heterocyclic, and alkynyl groups can be unsubstituted or substituted by halo, hydroxy, C₁-C₆ alkoxy, amino, nitro, C₁-C₄ alkylamino, di(C₁-C₄)alkylamino, C₃-C₆ cycloalkyl, phenyl, phenoxy, C₃-C₅ heteroaryl or heterocyclic radical, or C₃-C₅ heteroaryloxy or heterocyclic radical-oxy; or R_{6a} and R_{7a} taken

25 together with the N to which they are attached can complete a 5- to

- 10-membered cyclic ring, optionally containing one, two, or three additional heteroatoms selected from O, S, or NR_{10a}R_{11a}; or a pharmaceutically acceptable salt, ester, amide or prodrug thereof.
7. The anticancer combination of claim 6, wherein the MEK inhibitor has a structure of Formula (II) wherein R_{1a} is methyl, fluoro, or chloro; R_{2a} is H; R_{3a}, R_{4a}, and R_{5a} are each H or F; R_{6a} is H; R_{7a} is methyl, ethyl, 2-propenyl, propyl, butyl, pentyl, hexyl, cyclopropylmethyl, cyclobutyl methyl, cyclopropylmethyl, or cyclopropylethyl; and 4' position is I.
8. An anticancer combination comprising a mitotic inhibitor and a selective MEK 1 or MEK 2 inhibitor selected from:
- 4-Fluoro-N-hydroxy-2-(4-iodo-2-methyl-phenylamino)-benzamide;
- 4-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N-(methoxy)-benzamide;
- 4-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N-(prop-2-nyloxy)-benzamide;
- 4-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N-(2-phenoxyethoxy)-benzamide;
- 4-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N-(2-thienylmethoxy)-benzamide;
- 4-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N-(prop-2-enyloxy)-benzamide;
- 4-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N-(cyclopropylmethoxy)-benzamide;
- 4-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N-(cyclopentoxy)-benzamide;
- 3,4-Difluoro-2-(4-iodo-2-methyl-phenylamino)-N-(3-furylmethoxy)-benzamide;
- 3,4-Difluoro-2-(4-iodo-2-methyl-phenylamino)-N-ethoxy-benzamide;
- 3,4-Difluoro-2-(4-iodo-2-methyl-phenylamino)-N-(but-2-enyloxy)-benzamide;
- 3,4-Difluoro-2-(4-iodo-2-methyl-phenylamino)-N-(cyclopropylmethoxy)-benzamide;

- 3,4-Difluoro-2-(4-iodo-2-methyl-phenylamino)-N-(1-methylprop-
2-nyloxy)-benzamide;
- 3,4-Difluoro-2-(4-iodo-2-methyl-phenylamino)-N-(3-phenylprop-
2-nyloxy)-benzamide;
- 5 3,4-Difluoro-2-(4-iodo-2-methyl-phenylamino)-N-(3-methyl-5-phenylpent-
2-en-4-nyloxy)-benzamide;
- 3,4-Difluoro-2-(4-iodo-2-methyl-phenylamino)-N-(prop-2-nyloxy)-
benzamide;
- 3,4-Difluoro-2-(4-iodo-2-methyl-phenylamino)-N-(propoxy)-benzamide;
- 10 3,4-Difluoro-2-(4-iodo-2-methyl-phenylamino)-N-(cyclobutyloxy)-
benzamide;
- 3,4-Difluoro-2-(4-iodo-2-methyl-phenylamino)-N-(2-thienylmethoxy)-
benzamide;
- 3,4-Difluoro-2-(4-iodo-2-methyl-phenylamino)-N-(2-methyl-prop-
2-nyloxy)-benzamide;
- 15 3,4-Difluoro-2-(4-iodo-2-methyl-phenylamino)-N-(2-phenoxyethoxy)-
benzamide;
- 3,4-Difluoro-2-(4-iodo-2-methyl-phenylamino)-N-(but-2-nyloxy)-
benzamide;
- 20 3,4-Difluoro-2-(4-iodo-2-methyl-phenylamino)-N-(but-3-nyloxy)-
benzamide;
- 3,4-Difluoro-2-(4-iodo-2-methyl-phenylamino)-N-(cyclopentyloxy)-
benzamide;
- 3,4-Difluoro-2-(4-iodo-2-methyl-phenylamino)-N-(3-(2-fluorophenyl)-
prop-2-nyloxy)-benzamide;
- 25 5-Bromo-3,4-difluoro-N-hydroxy-2-(4-iodo-2-methyl-phenylamino)-
benzamide;
- 5-Bromo-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-N-(n-propoxy)-
benzamide;
- 30 5-Bromo-3,4-difluoro-N-(furan-3-ylmethoxy)-2-(4-iodo-2-methyl-
phenylamino)-benzamide;

- 5-Bromo-N-(but-2-enyloxy)-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-benzamide
- 5-Bromo-N-butoxy-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-benzamide;
- 5 5-Bromo-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-N-(3-methyl-but-2-enyloxy)-benzamide;
- 5-Bromo-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-N-(3-methyl-pent-2-en-4-nyloxy)-benzamide;
- 10 5-Bromo-3,4-difluoro-2-(4-iodo-2-methyl-benzyl)-N-[5-(3-methoxy-phenyl)-3-methyl-pent-2-en-4-nyloxy]-benzamide;
- 5-Bromo-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-N-(prop-2-nyloxy)-benzamide;
- 5-Bromo-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-N-[3-(3-methoxy-phenyl)-prop-2-nyloxy]-benzamide;
- 15 5-Bromo-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-N-(thiopen-2-ylmethoxy)-benzamide;
- 5-Bromo-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-N-(pyridin-3-ylmethoxy)-benzamide;
- 5-Bromo-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-N-(3-(2-fluorophenyl)-prop-2-nyloxy)-benzamide;
- 20 5-Bromo-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-N-(ethoxy)-benzamide;
- 5-Bromo-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-N-(cyclopropylmethoxy)-benzamide;
- 25 5-Bromo-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-N-(isopropoxy)-benzamide;
- 5-Bromo-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-N-but-3-nyloxy)-benzamide;
- 5-Chloro-N-hydroxy-2-(4-iodo-2-methyl-phenylamino)-benzamide;
- 30 5-Chloro-2-(4-iodo-2-methyl-phenylamino)-N-(tetrahydro-pyran-2-yloxy)-benzamide;
- 5-Chloro-2-(4-iodo-2-methyl-phenylamino)-N-methoxy-benzamide;

4-Bromo-2-(4-iodo-2-methyl-phenylamino)-N-phenylmethoxy-benzamide;
4-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N-phenylmethoxy-benzamide;
5-Fluoro-N-hydroxy-2-(4-iodo-2-methyl-phenylamino)-benzamide;
5-Iodo-2-(4-iodo-2-methyl-phenylamino)-N-phenylmethoxy-benzamide;

5-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N-(tetrahydropyran-2-yloxy)-
benzamide;

3,4-Difluoro-2-(4-bromo-2-methyl-phenylamino)-N-(3-phenylprop-
2-nyloxy)-benzamide;

3,4-Difluoro-2-(4-bromo-2-methyl-phenylamino)-N-(3-furylmethoxy)-
benzamide;

3,4-Difluoro-2-(4-bromo-2-methyl-phenylamino)-N-(2-thienylmethoxy)-
benzamide;

3,4-Difluoro-2-(4-bromo-2-methyl-phenylamino)-N-(but-3-nyloxy)-
benzamide;

3,4-Difluoro-2-(4-bromo-2-methyl-phenylamino)-N-(2-methyl-prop-
2-enyloxy)-benzamide;

3,4-Difluoro-2-(4-bromo-2-methyl-phenylamino)-N-(but-2-enyloxy)-
benzamide;

3,4-Difluoro-2-(4-bromo-2-methyl-phenylamino)-N-(methoxy)-
benzamide;

3,4-Difluoro-2-(4-bromo-2-methyl-phenylamino)-N-(ethoxy)-benzamide;

3,4-Difluoro-2-(4-bromo-2-methyl-phenylamino)-N-(cyclobutoxy)-
benzamide;

3,4-Difluoro-2-(4-bromo-2-methyl-phenylamino)-N-(isopropoxy)-
benzamide;

3,4-Difluoro-2-(4-bromo-2-methyl-phenylamino)-N-(2-phenoxyethoxy)-
benzamide;

3,4-Difluoro-2-(4-bromo-2-methyl-phenylamino)-N-(cyclopropyl-
methoxy)-benzamide;

3,4-Difluoro-2-(4-bromo-2-methyl-phenylamino)-N-(n-propoxy)-
benzamide;

- 3,4-Difluoro-2-(4-bromo-2-methyl-phenylamino)-N-(1-methyl-prop-
2-ynyl)benzamide;
- 3,4-Difluoro-2-(4-bromo-2-methyl-phenylamino)-N-(3-(3-fluorophenyl)-
prop-2-ynyl)benzamide;
- 5 3,4-Difluoro-2-(4-bromo-2-methyl-phenylamino)-N-(4,4-dimethylpent-
2-ynyl)benzamide;
- 3,4-Difluoro-2-(4-bromo-2-methyl-phenylamino)-N-(cyclopentoxy)-
benzamide;
- 3,4,5-Trifluoro-N-hydroxy-2-(4-iodo-2-methyl-phenylamino)-benzamide;
- 10 5-Chloro-3,4-difluoro-N-hydroxy-2-(4-iodo-2-methyl-phenylamino)-
benzamide;
- 5-Bromo-3,4-difluoro-2-(2-fluoro-4-iodo-phenylamino)-N-hydroxy-
benzamide;
- N-Hydroxy-2-(4-iodo-2-methyl-phenylamino)-4-nitro-benzamide;
- 15 3,4,5-Trifluoro-2-(2-fluoro-4-iodo-phenylamino)-N-hydroxy-benzamide;
- 5-Chloro-3,4-difluoro-2-(2-fluoro-4-iodo-phenylamino)-N-hydroxy-
benzamide;
- 5-Bromo-2-(2-chloro-4-iodo-phenylamino)-3,4-difluoro-N-hydroxy-
benzamide;
- 20 2-(2-Fluoro-4-iodo-phenylamino)-N-hydroxy-4-nitro-benzamide;
- 2-(2-Chloro-4-iodo-phenylamino)-3,4,5-trifluoro-N-hydroxy-benzamide;
- 5-Chloro-2-(2-chloro-4-iodo-phenylamino)-3,4-difluoro-N-hydroxy-
benzamide;
- 5-Bromo-2-(2-bromo-4-iodo-phenylamino)-3,4-difluoro-N-hydroxy-
benzamide;
- 25 2-(2-Chloro-4-iodo-phenylamino)-N-hydroxy-4-methyl-benzamide;
- 2-(2-Bromo-4-iodo-phenylamino)-3,4,5-trifluoro-N-hydroxy-benzamide;
- 2-(2-Bromo-4-iodo-phenylamino)-5-chloro-3,4-difluoro-N-hydroxy-
benzamide;
- 30 2-(2-Bromo-4-iodo-phenylamino)-N-hydroxy-4-nitro-benzamide;
- 4-Fluoro-2-(2-fluoro-4-iodo-phenylamino)-N-hydroxy-benzamide;
- 3,4-Difluoro-2-(2-fluoro-4-iodo-phenylamino)-N-hydroxy-benzamide;

2-(2-Chloro-4-iodo-phenylamino)-4-fluoro-N-hydroxy-benzamide;
2-(2-Chloro-4-iodo-phenylamino)-3,4-difluoro-N-hydroxy-benzamide;
2-(2-Bromo-4-iodo-phenylamino)-4-fluoro-N-hydroxy-benzamide;
2-(2-Bromo-4-iodo-phenylamino)-3,4-difluoro-N-hydroxy-benzamide;

5 N-Cyclopropylmethoxy-3,4,5-trifluoro-2-(4-ido-2-methyl-phenylamino)-
benzamide;

10 5-Chloro-N-cyclopropylmethoxy-3,4-difluoro-2-(4-ido-2-methyl-
phenylamino)-benzamide;

15 5-Bromo-N-cyclopropylmethoxy-3,4-difluoro-2-(2-fluoro-4-ido-
phenylamino)-benzamide;

N-Cyclopropylmethoxy-2-(4-ido-2-methyl-phenylamino)-4-nitro-
benzamide;

N-Cyclopropylmethoxy-3,4,5-trifluoro-2-(2-fluoro-4-ido-phenylamino)-
benzamide;

20 5-Chloro-N-cyclopropylmethoxy-3,4-difluoro-2-(2-fluoro-4-ido-
phenylamino)-benzamide;

5-Bromo-2-(2-chloro-4-ido-phenylamino)-N-cyclopropylmethoxy-
3,4-difluoro-benzamide;

N-Cyclopropylmethoxy-2-(2-fluoro-4-ido-phenylamino)-4-nitro-
benzamide;

25 2-(2-Chloro-4-ido-phenylamino)-N-cyclopropylmethoxy-3,4,5-trifluoro-
benzamide;

5-Chloro-2-(2-chloro-4-ido-phenylamino)-N-cyclopropylmethoxy-
3,4-difluoro-benzamide;

5-Bromo-2-(2-bromo-4-ido-phenylamino)-N-ethoxy-3,4-difluoro-
benzamide;

2-(2-Chloro-4-ido-phenylamino)-N-ethoxy-4-nitro-benzamide;

2-(2-Bromo-4-ido-phenylamino)-N-cyclopropylmethoxy-3,4,5-trifluoro-
benzamide;

30 2-(2-Bromo-4-ido-phenylamino)-5-chloro-N-cyclopropylmethoxy-
3,4-difluoro-benzamide

- 2-(2-Bromo-4-iodo-phenylamino)-N-cyclopropylmethoxy-4-nitrobenzamide;
- N-Cyclopropylmethoxy-4-fluoro-2-(2-fluoro-4-iodo-phenylamino)-benzamide;
- 5 N-Cyclopropylmethoxy-3,4-difluoro-2-(2-fluoro-4-iodo-phenylamino)-benzamide;
- 2-(2-Chloro-4-iodo-phenylamino)-N-cyclopropylmethoxy-4-fluorobenzamide;
- 2-(2-Chloro-4-iodo-phenylamino)-N-cyclopropylmethoxy-3,4-difluorobenzamide;
- 10 2-(2-Bromo-4-iodo-phenylamino)-N-cyclopropylmethoxy-4-fluorobenzamide; or
- 2-(2-Bromo-4-iodo-phenylamino)-N-cyclopropylmethoxy-3,4-difluorobenzamide.
- 15 9. The combination according to Claim 1 wherein the MEK inhibitor is a MEK1 or MEK 2 inhibitor selected from:
- 2-(2-chloro-4-iodophenylamino)-N-cyclopropylmethoxy-3,4-difluorobenzamide;
- 2-(2-methyl-4-iodophenylamino)-N-hydroxy-4-fluorobenzamide;
- 20 2-(2-methyl-4-iodophenylamino)-N-hydroxy-3,4-difluoro-5-bromobenzamide;
- 2-(2-methyl-4-iodophenylamino)-N-cyclopropylmethoxy-3,4-difluoro-5-bromobenzamide;
- 2-(2-methyl-4-iodophenylamino)-N-cyclobutylmethoxy-3,4-difluoro-5-bromobenzamide;
- 25 2-(2-chloro-4-iodophenylamino)-N-cyclopropylmethoxy-3,4-difluoro-5-bromobenzamide;
- 2-(2-chloro-4-iodophenylamino)-N-hydroxy-3,4-difluoro-5-bromobenzamide;
- 2-(2-chloro-4-iodophenylamino)-N-cyclobutylmethoxy-3,4-difluoro-
- 30 3,4-difluorobenzamide;

- 2-(2-chloro-4-iodophenylamino)-N-hydroxy-4-fluorobenzamide;
2-(2-methyl-4-iodophenylamino)-N-hydroxy-3,4-difluorobenzamide;
2-(2-methyl-4-iodophenylamino)-N-cyclopropylmethoxy-
3,4,5-trifluorobenzamide; and
5 2-(2-chloro-4-iodophenylamino)-N-cyclopropylmethoxy-
 4-fluorobenzamide.
10. An anticancer combination comprising paclitaxel and the MEK inhibitor
 2-(2-chloro-4-iodophenylamino)-N-cyclopropylmethoxy-
 3,4-difluorobenzamide.
- 10 11. A method for treating cancer in a patient, said method comprising
 administering to a patient in need of treatment a mitotic inhibitor and
 administering to said patient a MEK inhibitor, wherein the amount of the
 mitotic inhibitor and the amount of the MEK inhibitor are such that the
 combination is an effective anticancer therapy.
- 15 12. A method of claim 11, wherein the administration of the mitotic inhibitor
 and the administration of the MEK inhibitor are not simultaneous.
13. A method according to Claim 11 wherein the MEK inhibitor is a phenyl
 amine of Formula I.
14. A method according to Claim 11 wherein the MEK inhibitor is a phenyl
 amine of Formula II.
- 20 15. A method according to Claim 11 wherein the MEK inhibitor used in
 combination with a mitotic inhibitor is a selective MEK 1 or MEK 2
 inhibitor.
16. A method according to claim 15, wherein the MEK inhibitor is a
 compound selected from:
25

2-(2-chloro-4-iodophenylamino)-N-cyclopropylmethoxy-3,4-difluorobenzamide;
2-(2-methyl-4-iodophenylamino)-N-hydroxy-4-fluorobenzamide;
2-(2-methyl-4-iodophenylamino)-N-hydroxy-3,4-difluoro-
5
5-bromobenzamide;
2-(2-methyl-4-iodophenylamino)-N-cyclopropylmethoxy-3,4-difluoro-
5-bromobenzamide;
2-(2-methyl-4-iodophenylamino)-N-cyclobutylmethoxy-3,4-difluoro-
5-bromobenzamide;
10
2-(2-chloro-4-iodophenylamino)-N-cyclopropylmethoxy-3,4-difluoro-
5-bromobenzamide;
2-(2-chloro-4-iodophenylamino)-N-hydroxy-3,4-difluoro-
5-bromobenzamide;
2-(2-chloro-4-iodophenylamino)-N-cyclobutylmethoxy-
15
3,4-difluorobenzamide;
2-(2-chloro-4-iodophenylamino)-N-hydroxy-4-fluorobenzamide;
2-(2-methyl-4-iodophenylamino)-N-hydroxy-3,4-difluorobenzamide;
2-(2-methyl-4-iodophenylamino)-N-cyclopropylmethoxy-
3,4,5-trifluorobenzamide; and
20
2-(2-chloro-4-iodophenylamino)-N-cyclopropylmethoxy-
4-fluorobenzamide.

17. The method according to Claim 11 wherein the mitotic inhibitor is selected from paclitaxel, docetaxel, vincristine, vinblastine, vinorelbine, and vinflunine.
- 25
18. The method according to Claim 17 wherein the mitotic inhibitor is paclitaxel.
19. The method according to Claim 17 wherein the mitotic inhibitor is docetaxel.

20. The method according to Claim 17 wherein the mitotic inhibitor is vincristine.
21. The method according to Claim 17 wherein the mitotic inhibitor is vinblastine.
- 5 22. The method according to Claim 17 wherein the mitotic inhibitor is vinorelbine.
23. The method according to Claim 17 wherein the mitotic inhibitor is vinflunine.
24. The method according to Claim 17 wherein the MEK inhibitor is 2-(2-chloro-4-iodophenylamino)-N-cyclopropylmethoxy-3,4-difluorobenzamide.
- 10 25. A method according to Claim 16, wherein the mitotic inhibitor is paclitaxel, docetaxel, or vincristine.

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